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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/027,654	02/23/98	HORTON J	28911/34561

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EXAMINER	
GAREL, G	
ART UNIT	**PAPER NUMBER**
1641	11

DATE MAILED: 12/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/027,654	HORTON, JEFFREY KENNETH	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *28 September 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 9/28/00 is acknowledged and has been entered. Claims 1, 4, and 14 have been amended. Claim 3 has been canceled. Claims 19-20 have been added. Claims 1-2, and 4-18 are pending and under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-2 and 4-20 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as amended, is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, it is unclear what structural and functional cooperative relationships exist between the elements or absence thereof (assay reagents, i.e. tracer / label) in claim 1 and the claimed "assay reagents" in the subsequent claims 17 and 18.

Claim 6 is vague and confusing in reciting "individual assays are performed in parallel ... " because it does not clearly and distinctly define what is encompassed by

the phrase "individual assays". Are these individual assays of the same type and from a same sample (source), from different samples assayed simultaneously, 3) different types of assays (scintillation proximity assay or immunoassay) performed at the same time, as reflected by the different types of assays in claims 8, 9, and 10. It is further unclear how "the assay(s) of step (ii)" in claims 8 and 9 differ from and relate to "the specific binding assay of step (ii)" in claim 10, the "specific binding assay ... " in claim 15, and the "receptor binding assay" in claim 16 in as far as the "individual assays" are concerned because all claims aforementioned appears to require and relate back to the same "specific binding partner" in claim 1.

Claim 17 lacks sufficient antecedent support in reciting "the assay reagents" based on amended claim 1.

Claim 18 lacks sufficient antecedent support in reciting "the assay reagents" based on amended claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Upon further consideration, the rejection of claims 1-4, 8-11, and 13-14 under 35 U.S.C. 103(a) as being unpatentable over Cook (1) (Research Focus, 1996) in view of Lundin (US 5,558,986) is withdrawn.

4. Upon further consideration, the rejection of claims 1 and 15-18 under 35 U.S.C. 103(a) as being unpatentable over Cook (1) (Research Focus, 1996) in view of Lundin (US 5,558,986), and in further view of Cook (2) (WO 94/26413) is withdrawn.

New Grounds of Rejection

5. Claims 1, 2, 4, 5, 8-11, and 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook (1) (Research Focus, 1996) in view of Lundin (US 5,558,986).

Cook (1) teach that scintillation proximity assay is an established high-throughput screening technology that allows the design of high-flux assays for a variety of biochemical and cellular targets which requires no separation and relies entirely on "mix and measure" format (see Abstract). Scintillation proximity assay (SPA) which is homogeneous in nature has been applied to various specific binding interactions which includes cellular adhesion molecule binding, protein-peptide or antigen-antibody interactions, and cellular biochemistry assays (see page 2, column 2, first paragraph and page 4, column 2). In SPA, the analyte is immobilized to a small scintillant-containing microsphere and a radioisotopically labeled molecule binds to the microsphere, and the radioisotope is brought into close proximity to the scintillant and effective energy transfer from the particle will take place (see page 3, column 1). The

SPA microspheres therefore replace the traditional separation steps employed in radioimmunoassay (see Figures 1 and 2). Cook teach that the technology has been used with a broad spectrum of applications including mass measurements in cellular function screening for analytes such as prostaglandins, interleukins, and adenosine-3',5'- cyclic monophosphate (cyclic AMP). Box 1 in page 4 illustrates examples of radioimmunoassay developed using SPA and box 2 in page illustrates examples of receptor-ligand binding assays developed using SPA. Cook (1) fails to teach incorporation of a detergent such as dodecyl trimethyl ammonium bromide and a neutralizing agent such as cyclodextrin.

Lundin disclose a method of extracting analyte (intracellular components) from a cellular sample by mixing the sample of cells with a lysis reagent (extractant) to generate a lysed cellular sample (extract solution) and simultaneously contacting the lysed cellular sample with a sequestrant such as cyclodextrin or a derivative thereof, to sequester (neutralize) the lysis reagent (see Abstract and column 6, lines 38-49). The lysis reagent used conventionally is detergent (see column 2, lines 43-45). Lundin teach that lysis reagents that rapidly open up cell membranes also simultaneously inactivate enzymes that act on intracellular components causing considerable metabolite changes and therefore separation (removal) of the detergent is necessary (see column, lines 32-48 and column 2, lines 43-48). Cyclodextrin sequesters the lysis reagent by forming a complex with it wherein it is possible but not necessary or desirable to remove the complex from the solution (see column 5, lines 33-52 and

column 6, lines 55-67). Cyclodextrin is preferably used in excess of the surfactant on a molar basis considering the stoichiometry of inclusion complex that is formed. Lundin disclose that any lysis reagent and any cyclodextrin may be used as long as the inhibition or inactivation of enzymes is avoided for use in assay procedures. The lysis reagent is preferably a surfactant contacted with which is mixed with α, β, or γ cyclodextrin (see column 7, lines 13-37). The cyclodextrin can be added at any step in the assay method after completion of lysis but always before or simultaneously with the addition of specific binding partners (enzymes) involved in the assay (column 7, lines 28-38). Lysis reagents are selected among various surfactants which include dodecyl trimethyl ammonium bromide (Example 1). The analytes extracted from cells may include intracellular metabolites such as ATP and nucleic acids. Lundin further disclose a kit for lysis and assay of analytes, i.e. ATP comprising a lysis reagent, a cyclodextrin, reagent with specific binding partner, i.e. firefly luciferase reagent, and an assay buffer (see column 7, lines 3-13).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine a detergent such as dodecyl trimethyl ammonium bromide to lyse cellular membranes and a sequestrant such as cyclodextrin for simultaneously neutralizing the detergent as taught by Lundin into the scintillation proximity assays of Cook (1) in order to measure concentration of intracellular and extracellular analytes because Cook (1) specifically taught measuring intracellular and extracellular analyte function in his assay and Lundin disclosed that extraction of analytes from cellular

samples while maintaining their functional integrity for use in immunological assays is difficult but can be overcome by use of dodecyl trimethyl ammonium bromide and cyclodextrin which provide efficient extraction and neutralization agents, respectively, to obtain better and more accurate cellular analyte function measurements. One of ordinary skill in the art would have been motivated to combine the teaching of Lundin in extraction of cellular components and neutralization of the extractant with the many scintillation proximity assay applications as discussed by Cook (1) because Lundin specifically taught efficient analyte separation of his method in homogenous assays and Cook (1) specifically taught advantages of not requiring separation in SPA including convenience, ease, economy and safety from potential hazardous or radioactive materials due to minimal handling thereof.

One of ordinary skill in the art would have reasonable expectation of success in selecting the amount of sequestrant used in neutralizing the lysis reagent because reagent concentration selection is conventional and well known in the art. Furthermore, appropriate reagent concentration selections are result effective variables which are dependent upon scientific data acquired resulting from experimentation pursuant to optimization, and standardization of procedures.

6. Claims 6-7 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook (1) (Research Focus, 1996) in view of Lundin (US 5,558,986), and in further view of Cook (2) (WO 94/26413).

Cook (1) and Lundin have been discussed supra. Cook (1) and Lundin fail to teach use of a multiwell system for use in both culturing cells and assaying cellular analyte.

Cook (2) disclose an apparatus and method for studying cellular processes using scintillation proximity assay. The apparatus comprises a vessel having a base with a scintillant substance and which is adapted for attachment and growth of cells (see Abstract). Cook (2) further disclose a multiwell plate comprising an array of wells held in fixed relationship to one another wherein each well is a vessel (see page 10, first full paragraph). The scintillant substance include aromatic hydrocarbons which emit light used for detection. The method of studying cellular processes includes introducing into the vessel a sample of cells labeled with a radioisotope emitting electrons, and using detection means to observe scintillation caused by radioactive decay so as to study the cellular process (see page 10, second full paragraph). The multiwell plate can take various formats for the purpose of culturing cells using standard cell culture media and growing cells in a sterile environment at 37 C in a 95 % humidified air and 5% CO2 incubator as well as studying cellular biochemical processes in living cells (page 14, second and third full paragraphs and page 15, second full paragraph). Cook (2) disclose that the surface of wells or vessels in the microwell plate requires modification in order to be adapted for the attachment and/or growth of cells. Cook (2) disclose that a considerable advantage of the scintillation proximity assay is that it does not require

separation of bound and molecular species from free, thereby minimizing handling of potentially hazardous substances (see page 7, second full paragraph).

It would have been obvious to one of ordinary skill in the art to incorporate that use of a multiwell system with an array of reaction vessels as taught by Cook (2) into the teachings of Cook (1) and Lundin supra because it allows for minimal handling of materials in high-throughput immunoassay testing and Cook (1) specifically taught the need for rapid, high flux simultaneous homogeneous assays. One of ordinary skill in the art would have been motivated to incorporate derivatized multiwell systems of Cook (2) into the method of Cook (1) and Lundin because of the high capacity yet efficient system achievable in assaying a wide variety of biochemical and cellular analytes for screening and identification.

Response to Arguments

7. A) Applicant argues that there is no teaching in the art that a cyclodextrin is used as sequestrant for cell lysis agents in specific binding assays. Applicant further argues that Lundin only teaches an enzyme assay where the complexed agent is not the intracellular agent and does not teach its use in the context of specific binding assays.

Contrary to Applicant's argument, while Lundin specifically taught cyclodextrin as a sequestrant for cell lysis agents for use in enzyme assays, the advantage achieved in its use with the lysis agent in the enzyme assay comes from its high binding affinity with the lysis agent; thus, reducing possibility of interference with the components in the

enzyme assay. For that reason, one of ordinary skill in the art at the time of the instant invention would have a reasonable expectation of success and predictability in using the same lysis-sequestrant combination in a specific binding assay such as taught by Cook (1) in order to prevent interference with specific binding components in homogenous assay binding systems due to the known high binding affinity between the lysis agent and cyclodextrin combination such as taught by Lundin.

8. Applicant's amendment and arguments have been considered but are not deemed persuasive. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gail Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

12/3/00

Gail Gabel
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12/04/00